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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Continuation Sheet (PTOL-303)

Continuation of 11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because:

Claims 11, 12, and 20-28 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the Office Actions of 11/21/05, 11/30/06, 1/4/08, 12/17/08, 6/11/09, 8/25/09, and 12/10/09, and for the reasons set forth below, because the specification, while being enabling for a method of ameliorating brain damage associated with epilepsy or stroke in a mammal, via prior oral administration of an AAV vector comprising a nucleic acid encoding NMDAR1 operably linked to a promoter, such that the antigen is expressed and elicits production of NMDAR1-specific antibodies in the circulatory system of the mammal, wherein epileptic seizures are diminished and stroke infarct volume is decreased as compared to an untreated control mammal, does not reasonably provide enablement for a method of ameliorating epilepsy or stroke in a mammalian subject by administration of any vector encoding an NMDA receptor-1 antigen, by any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At page 6 of the response, Applicant asserts that the specification is enabling for the broader scope of *mammalian* subjects as defined in the specification, including humans. The arguments presented at pages 6-7 are convincing and therefore the scope of enablement has been broadened to include **all mammals.**

At page 7 of the response, Applicant asserts that the specification, while presenting only experimental results with an oral composition, fully enables other modes of administration as well. Applicant again points to sections III and IV of the specification. Applicant points to methods of delivery listed in section III and section IV "Delivery Systems" of the specification, in which alternative delivery mechanisms such as intravenous and intramuscular injection are taught. However, the availabilty of other modes of administration is not sufficient to enable the use of other modes of administration in the claimed

invention because McCluskie amply demonstrates that different modes of administration produce varying effects that are not predictable. Accordingly, there is no evidence that these other modes of administration would evoke a therapeutic effect to ameliorate epilepsy or stroke in a subject.

At page 8 of the response, Applicant alleges that Li et al. (2005), Roy et al. (2000), and Tollefsen et al. (2003) used different routes of administration and obtained efficacy in rodents, larger mammals, and humans regardless of administration route. While Li et al. (2005) teach the administration of plasmid DNA by intramuscular injection 5 days after intramuscular inoculation with cardiotoxin, followed by a booster at 1 week, the instant specification does not provide any guidance with regard to the use of plasmids, or routes of administration suited to plasmid DNA, and since Li et al. is post-filing art, one of skill in the art would not have had the benefit of the teachings of Li et al. at the time of the instant invention. Roy et al. (2000) provide guidance with regard to bombardment with DNA-coated gold particles, but again, the reference is post-filing art and thus, one of skill in the art would not have had the benefit of the teachings of Roy et al. at the time of the instant invention. Tollefsen et al. (2003) provide guidance regarding the injection of plasmid DNA. The reference is directed to a study of injection of plasmid DNA with and without electroporation. The study demonstrated improved T cell responses after electroporation, but again, the reference is post-filing art and thus, one of skill in the art would not have had the benefit of the teachings of Tollefsen et al. at the time of the instant invention. Thus, while the post-filing art describes the development and evaluation of other modes of administration, with plasmid DNA, the skilled artisan would not have had the benefit of those teachings at the time of the instant invention.

In the supplemental response filed June 14, 2010, Applicant alleges that the specification enables the use of vectors other than AAV because the specification is replete with teachings and examples for use of different vector systems. Applicant again points to section IV of the specification which is directed to "Delivery Systems" and the discussion of the uses of different vectors. Applicant alleges that, based on

these teachings, one of ordinary skill in the art would be capable of utilizing an array of vectors or delivery systems. Applicant further alleges that one of ordinary skill in the art, having familiarity with AAV vectors, would have knowledge to make and use other vectors or delivery compositions. However, since other vectors or delivery compositions would be understood to produce unpredictable results, the skilled artisan would recognize that each vector must be tested individually to identify appropriate parameters (e.g., promoter, expression control sequences, routes of administration, schedules of administration, adjuvants, etc.) that would work in concert to produce the desired result of ameliorating epilepsy or stroke in a mammalian subject. Given the large number of possible combinations, such individual testing rises to the level of undue experimentation. Furthermore, the availability of other vectors is not sufficient to enable the use of other vectors in the claimed methods because the art of record demonstrates that finding the appropriate vector, with the appropriate control sequences, under the appropriate mode of administration to provide a therapeutic effect, is unpredictable. Giving due consideration to all the *Wands* factors, including but not limited to, the unpredictability in the art of DNA vaccination, it is maintained that the specification fails to enable the use of vectors other than AAV. See especially the evidence cited and discussed at pages 6-11 of the Office action of 11/21/05, which details the difficulties intrinsic to designing appropriate vectors for genetic immunization protocols sufficient to produce a therapeutic effect.

At page 3 of the supplemental response, Applicant alleges that Appendices A-C, submitted with the response on June 10, 2010, demonstrated the utilization of different vector systems that were capable of producing an immune response to the DNA antigen in either animals or humans. Applicant concludes that limiting the claims to AAV vectors is unnecessarily narrowing an improper in light of the teachings of the specification and knowledge of one of ordinary skill in the art. However, as noted hereinabove, the references of Li et al. (2005), Roy et al. (2000), and Tollefsen et al. (2003) are post-filing art, and therefore the teachings of Li et al. (2005), Roy et al. (2000), and Tollefsen et al. (2003) would not have

been available to one of skill in the art at the time of the instant invention, and thus the skilled artisan would not have had the benefit of the teachings of those references in determining how to extrapolate from the AAV vector to construct other vectors that would produce the same type of therapeutic effect in ameliorating both stroke and epilepsy. Given the evidence of record, it is clear that evoking an antibody response at any level, is not sufficient to provide the biological effects recited in the claims. While the evidence of record shows that an AAV vector can produce the recited biological effects, the results that may be produced using other vectors, delivered by other routes of administration are unpredictable, for reasons of record.

A complete *Wands* analysis has been provided, with a discussion of those factors most relevant to the present claims, including the nature of the invention, the state of the prior art, the predictability of the art, the breadth of the claims, the amount of direction or guidance presented, the presence or absence of working examples, and the quantity of experimentation necessary to enable the claims over their full scope. Giving due consideration to all the *Wands* factors, it was concluded that the specification fails to provide an enabling disclosure for the full scope of the claims. Numerous references were provided pointing to the unpredictability in the art of DNA vaccination and it is maintained that the specification fails to enable the full scope of the claims.

Given the *Wands* analysis of record, the specification fails to enable the full scope of the claims. The court has stated that "[n]aturally, the specification must teach those of skill in the art how to make and use the invention as broadly as it is claimed." *In re Goodman*, 29 USPQ2d 2010 at 2013 (Fed. Cir. 1993).

The unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman,* 29

USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991).

Thus, it is maintained that the specification fails to enable the full scope of the claims.